REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1-18 and 33-49 are pending in this application. Claims 1-18 and 33-49 have been rejected. Claims 1, 3, 11, 14, 38, 45 and 46 has been amended. Support for the amendment to claim 1 appears in the specification at, e.g., page 8, lines 5-7. No new matter is added.

Applicants have cancelled claims 19-32 as drawn to non-elected inventions. Applicants reserve the right to pursue the subject matter of these claims in a later application.

Double Patenting Rejections

Claims 5, 8-10, 12-18, 43-44 and 46-49 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as claims 1, 20-22, 25-27, 29, 31-33, 58-59, 61, 63, 65 and 66 of copending Application No. 10/256,023. Applicants will cancel claims 1, 20-22, 25-27, 29, 31-33, 58-59, 61, 63, 65 and 66 of U.S.S.N. 10/256,023 or claims 5, 8-10, 12-18, 43-44 and 46-49 of the instant application upon a notice of allowable subject matter. Withdrawal of this rejection is requested.

Claims 1-4, 6-7, 11, 33-42 and 45 have been provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8-9, 11, 14-15, 24, 27-56 and 60 of copending Application No. 10/256,023. Applicant files a terminal disclaimer in compliance with 37 C.F.R. §1.321(c) herewith. Withdrawal of this rejection is requested.

Rejection under 35 U.S.C. §112

Claims 1-18 and 33-49 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention (*See*, Office Action at page 5). Specifically, the Examiner states that the breadth of the claims is such that any lipophilic vitamin, antibiotic or hormone forms a complex with any natural polysaccharide but that no specific guidance is provided beyond a description in

generic terms (*See*, Office Action at pages 5-7). The rejection is traversed to the extent it is applied to the claims as amended.

Claim 1, as amended herein, and dependent claims 2-7 are drawn to a hydrophilic inclusion complex comprising water-insoluble lipophilic particles and an amphiphilic polymer which consists of a single amphiphilic polymer. Similarly, independent claim 8, from which depends claims 9-18, independent claim 33, from which depends claims 24-42, and claim 43, from which depends claims 44-49, are drawn to a method of forming a hydrophilic inclusion complex that includes water-insoluble lipophilic particles and an amphiphilic polymer.

The test for determining whether a claim fulfills the written description requirement is set forth in Amgen Inc. v. Hoechst Marion Roussel, Inc.[1]:

> The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed'.

An objective standard for determining compliance with written description is whether the disclosure of the application relied upon reasonably conveys to persons of ordinary skill in the art that the Applicant had possession of the claimed subject matter as of the date of the invention.[2,3]

The specification adequately describes to one of ordinary skill in the art the claimed subject matter, *i.e.,* an inclusion complex comprising any insoluble lipophilic particles and a variety of water-soluble polymer and methods of forming the same. The specification describes that a water-insoluble lipophil, irrespective of molecular mass, molecular weight, or functional groups, can be complexed with a water-soluble polymer to create an inclusion complex which renders the complex hydrophilic in water (*See*, specification at page 7, line 19 - page 8, line 7). The specification also describes various polymers (*See*, specification at page 8, lines 7-11). The specification further

[1] 314 F.3d 1313 , 65 USPQ2d 1385, (Fed. Cir. 2003) (internal citations omitted)
[2] *In re Kaslow*, 707 F.2d 1366 (Fed. Cir. 1983)
[3] *In re Gosteli*, 872 F.2d. 1008 (Fed. Cir. 1989)

describes the steps required to prepare the recited inclusion complex (*See*, specification at page 13, lines 14-30; page 17, line 16 - page 19, line 9).

The specification also describes an adequate representative species of insoluble lipophilic particles (peptides and polypeptides, nucleotides and co-ferments, vitamins, steroids, porphyrins, metal-complexes, purines, pyrimidines, antibiotics or hormones) and an adequate representative species of water-soluble polymers (natural polysaccharides, polyacrylic acid and its derivatives, polyethylene imine and its derivatives. polymethacrylic acid and its derivatives, polyethylene oxide and its derivatives, polyvinyl alcohol and its derivatives, polyacetylene derivatives, polyisoprene derivatives and polybutadiene derivatives) (*See*, specification at page 8, lines 7-11; claims 3, 11 and 45 as originally filed). The claim terms "polymer" and "lipophil" or "lipophilic compound" are explained in sufficient detail in the specification that one of ordinary skill in the art can readily determine what is encompassed within Applicants' invention (*See*, specification at page 7, line 19 - page 8, line 11).

Table 1 at page 19 discloses a series of lipophilic drug reagents with varying properties (*i.e.* different molecular mass, molecular weight, functional groups, etc.) and a series of selected polymers with varying properties (*i.e.* molecular weight, chain length, solubility, hydrophilic-lipophilic balance, etc.) as well as specific solvents and process temperatures following the methods of forming an inclusion complex comprising water-insoluble lipophilic particles and an amphiphilic polymer described in the specification (*See*, specification at page 13, lines 14-30; page 17, line 16 - page 19, line 9).

Further, in the 37 C.F.R. § 1.132 declaration, included herewith, Dr. Rina Goldshtein states that the teachings of the instant specification were used to form hydrophilic inclusion complexes for various lipophilic compounds, such as, Clarithromycin, Azithromycin, Itraconazole and Taxol. For example, in one study results show that when the macrolide antibiotic, Clarithromycin, which is a poorly soluble hydrophobic compound, is surrounded by a polymer (*i.e.,* Alginat, PVA and Chitosan), using the lipophilic compound/amphiphilic polymer matching technique described in the instant application, the resulting inclusion complex is rendered hydrophilic (*See*, Appendix A). In a second study results show that when the macrolide antibiotic, Azithromycin, which is a poorly soluble hydrophobic compound, is surrounded by a polymer (*i.e.,* Alginat, PVA, Manucol Ester B, and Chitosan), using the lipophilic compound/amphiphilic polymer matching technique described in the instant application, the resulting inclusion complex is rendered hydrophilic (*See*, Appendix B).

In a third study results show that when the anti-fungal agent, Itraconazole, which is an insoluble compound, is surrounded by a polymer (*i.e.,* Thermo-destructed Starch combined with H_2O_2 and PEG, Alginat, and Chitosan), using the lipophilic compound/amphiphilic polymer matching technique described in the instant application, the resulting inclusion complex is rendered hydrophilic (*See*, Appendix C). In a fourth study results show that when the anti-cancer agent, Taxol, which is an insoluble compound, is surrounded by a polymer (B_{12}), using the lipophilic compound/amphiphilic polymer matching technique described in the instant application, the resulting inclusion complex is rendered hydrophilic (*See*, Appendix D). These results confirm the teachings of the specification and the results described in Table 1; and, additionally, demonstrate that Applicants had possession of the claimed invention.

Applicants submit that, based on the discussion *supra*, the 37 C.F.R. § 1.132 declaration of Dr. Rina Goldshtein and the instant specification, one of ordinary skill in the art would reasonably determine that the Applicant had possession of the claimed subject matter as of the date of the invention. The rejection should be withdrawn.

Rejections under 35 U.S.C §103

Claims 1-7 are rejected over the combination of Rolfes et al., U.S. Pat. No. 6,221,399 ("Rolfes"), in view of Parikh et al., U.S. Pat. No. 6,228,399 ("Parikh"). Specifically, the Examiner states that Rolfes teaches an interpolymer complex incorporating an active agent, which can be vitamins and antibiotics and polymers, which can include guar gum, cellulose, starches and xanthan gum. The Examiner further states that Rolfes teaches that complexation occurs via reversible physical molecular forces and excludes irreversible chemical forces such as covalent bonding and that the secondary reference (Parikh) teaches that microparticles (diameters from nanometers to micrometers) provide advantages over unformulated drug particles including improved oral bioavailability of drugs (*See*, Office Action at pages 8-9). Applicants traverse the rejection to the extent it is applied to the claims as amended.

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces the claimed invention; and (2) the prior art contains a suggestion or motivation to combine the prior art

references in such a way as to achieve the claimed invention.[4] The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention.[5] The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification.[6]

Claim 1 has been amended herein to recite "...an amphiphilic polymer, wherein said amphiphilic polymer consists of a single amphiphilic polymer..." Applicants submit that this feature of the claimed invention is not obvious over Rolfes in view of Parikh. Specifically, Rolfes describes a solid interpolymer matrix comprising complexes of two or more complementary polymers (*See*, Rolfes at column 7, lines 1-23). The reference further reports that the two complementary polymers, which are capable of complexing with each other, produce a precipitate or gel (*i.e.*, a physical 3-dimensional network is formed). However, Rolfes does not teach non-interpolymer complexes or inclusion complexes comprising a single amphiphilic polymer, as the amended claims expressly require. Claims 1-7 as amended herein are drawn to a hydrophilic inclusion complex comprising water-insoluble lipophilic particles and an amphiphilic polymer which consists of a single amphiphilic polymer. Unlike the present invention, Rolfes teaches complementary polymers or polymers which form interpolymer matrixes by complexing with each other. In addition, unlike the claimed invention, Rolfes teaches the formation of precipitates or gels. For this reason, Rolfes' requirement of interpolymer complexes teaches away from the present invention.

Furthermore, Rolfes describes the active agent as becoming incorporated into the interpolymer complex, *e.g.*, embedded or encapsulated in the interpolymer complex (*See*, Rolfes at column 7, lines 26-28 and lines 32-33). Specifically, the incorporation of the active agent into the interpolymer complex creates a viscous environment that encourages a homogeneous distribution of the dispersed drug within the polymer matrix. Rolfes does not teach direct complex formation between the polymer and the active agent, as claimed here. The claimed invention does not require incorporation of the active agent into an interpolymer complex. To the contrary, , the present invention claims hydrophilic inclusion complexes and methods of making them (by identification of polymers, using the disclosed algorithm),where the polymer forms a common single structure unit

[4] *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).
[5] *In re Napier*, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995).

with the lipophilic compound (*i.e.* a complex with non-valence bonds). This specific hydrophilic inclusion complex, which is directly formed between the polymer and lipophilic compound, may improve various properties of the lipophilic compound, such as increased solubility, amorphosity, increased bioavailability, etc.

Parikh does not cure the deficiencies of Rolfes. Parikh teaches is cited for describing the production of microparticles (particles having diameters from nano- to micrometers). Parikh does not teach or suggest non-interpolymer complexes or inclusion complexes comprising a single amphiphilic polymer, as claimed here. Further, Parikh teaches the addition of surfactants as a key component of the production of microparticles, whereas the nano-particles of the present invention do not employ surfactants (*See*, Parikh at column 1, line 60 - column 2, line 30).

In summary, Applicants submit that the combination of Rolfes and Parikh does not teach or suggest the claimed invention and that one of ordinary skill in the art combining the teachings of Rolfes and Parikh would not produce the present invention. In view of the above, withdrawal of the present rejection is respectfully requested.

[6] *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

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